



PATENT APPLICATION

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Applicant(s): Alice C. MARTINO, et al

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Scott L. Douglas, declare:

THAT, I received an A.A.S, degree in industrial Chemistry Technology from Ferris State University un 1969;

THAT, I joined the Upjohn Company in 1969;

THAT, I have worked in the drug delivery, formulation and pharmaceutical science areas of Pfizer, Inc. (and its predecessor companies Upjohn and Pharmacia) for more than 35 years. That work has included support of: (1) exploratory formulations, (2) product life cycle management, (3) solid forms and salt selection, (4) phase I formulation development, (5) drug candidate selection and discovery support (6) pre-formulation characterization of new candidate drugs, (7) animal model development for drug delivery, (8) analytical methods development (HPLC, UV, IR etc.) and (9) organic chemistry.

THAT, my present position with Pfizer is as a Research Chemist. Some of my recent assignments include, evaluation of

bead technology for use in drug delivery, product life cycle management, sustained release studies using film coated spheronized drug, small particle coating onto beads for immediate release drug delivery applications, studies on the characterization of films, the development of Sugen prodrugs for study in animals, studies on the formulation factors affecting drug release, solubilization, re-precipitation, and other processes relevant to intestinal absorption, *in vitro* delivery of drugs to the mesenteric lymph using the rat model, studies looking for drug release and re-precipitation of developmental candidates, annulated rat perfusion model with mesenteric blood collection for drug absorption;

THAT, I have authored or co-authored five external articles and more than one hundred twenty publications and technical reports within Pfizer.

That I have authored or co-authored more than 120 technical reports, hundreds of technical memos and many internal poster and oral presentations have been made. These list are available to Pfizer employees upon request.

THAT, being so qualified the declarant further states:

THAT, I have read the above captioned patent application and;

THAT

A RAPIDLY PRECIPITATING DRUG, AS THAT TERM IS USED IN THE ABOVE CAPTIONED APPLICATION CAN BE IDENTIFIED BY ONE SKILLED IN THE ART WITHOUT UNDUE EXPERIMENTATION

THAT, the phenomena of supersaturation is well known in the art and is described in many experimental chemistry textbooks. For example, Prutton et al, "Principles of Physical Chemistry", 1948, pp 141-142 (Exhibit SD-I), discloses:

"A solution which contains at a given temperature as much solute as it can hold in presence of the dissolving substance is said to be saturated. Any solution which contains less than this amount of solute is said to be unsaturated while if it contains more than this amount, it is supersaturated. A supersaturated solution can exist

only in the absence of dissolving substance, and is at best unstable. Jarring and stirring may, and introduction of solute will, cause the precipitation of excess solute in solution, leading to the formation of saturated solution. To determine the state of a solution with respect to saturation it is only necessary to introduce some of the dissolving substance. If the substance dissolves, the solution is unsaturated; if no further solubility takes place, the solution is saturated; while if precipitation takes place, the original solution was supersaturated. (Emphasis added)

THAT, whether or not a drug is prone to supersaturation in water or simulated physiological fluid at body temperature can be ascertained by determining whether a concentration of the drug that is higher than its saturation concentration can be attained in the fluid at body temperature. If a higher concentration is attained, the drug is prone to supersaturation;

THAT, procedures for measuring the concentration of a drug in solution and hence determining its solubility in solution are well known in the art as disclosed in Remington; 16th Edition, p.207, 2nd column, "*Method for Determining Solubilities*" (Exhibit SD-II);

That, one procedure for determining whether a drug is a rapidly precipitating drug would be to take an adult dose of the drug and put it into 120 ml of water at 37 degree C (body temperature). This situation would be equal to taking one dose with 6 oz of water. After adding the drug to the 37 degree liquid, stir and remove small samples every minute over a 1-2 hour period. The samples should then be filtered and assayed for drug in solution, using some analytical method such as HPLC;

THAT, the time for a drug to precipitate out of solution can be determined by visual observation or more accurately using conventional analytical equipment;

THAT, a drug is a rapidly precipitating drug if (1) it forms a higher concentration in water or other physiological

fluid at body temperature than its saturation concentration at body temperature and (2) its concentration goes down rapidly with time due to precipitation of the drug or its un-ionized equivalent;

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the application or patent issued thereon.

Dated: August 16, 2004

Scott L. Douglas
Scott L. Douglas



CHAPTER V

Solutions

Introduction. When several substances are mixed, three possible types of mixtures may be obtained: (1) a coarse mixture, such as that of salt and sugar; (2) a colloidal dispersion, such as results when fine clay is shaken with water; (3) a true solution, obtained when a substance like sugar dissolves in water. In the coarse mixture, the individual particles are readily discernible, and may be separated from each other by mechanical means. Although in a colloidal dispersion the particles are much finer and the heterogeneity is not so readily apparent, the dispersion is, nevertheless, not homogeneous, as will be shown in the chapter on colloids. On the other hand, in the true solution no heterogeneity can be detected, and the constituents cannot be separated from each other by mechanical means. Every part of the solution is found to be like every other part, i.e., a true solution constitutes a homogeneous phase.

We may, therefore, define a true solution as a *physically homogeneous mixture of two or more substances*. This definition of a solution places no restriction on either the state of aggregation or the relative amounts of the constituents, and consequently a solution may be gaseous, liquid, or solid, and may vary in composition within wide limits. It is this latter fact which excludes pure compounds from the classification of solutions, for a fixed and definite ratio persists among the constituents in a compound.

It is frequently convenient to refer to the substance that dissolves as the *solute*, and to the substance in which solution takes place as the *solvent*. For the solubility of solids in liquids, where the liquid is usually present in large excess over the solid, there is no ambiguity in these terms, the solid being the solute, the liquid the solvent. However, when dealing with the solubility of such liquids as acetone and water or dioxane and water, which dissolve in each other in all proportions, it is difficult to differentiate between solute and solvent. This difficulty will not arise in our discussions, for the terms will be employed only when there is no ambiguity as to meaning.

A solution which contains at a given temperature as much solute as it can hold in presence of the dissolving substance is said to be *saturated*.

Any solution which contains less than this amount of solute is said to be *unsaturated*, while if it contains more than this amount, it is *supersaturated*. A supersaturated solution can exist only in the absence of dissolving substance, and is at best very unstable. Jarring and stirring may, and introduction of solute will, cause the precipitation of excess solute in solution, leading to the formation of a saturated solution. To determine the state of a solution with respect to saturation it is only necessary to introduce some of the dissolving substance. If the substance dissolves, the solution is unsaturated; if no further solubility takes place, the solution is saturated; while if precipitation takes place, the original solution was supersaturated.

Factors Affecting Solubility. The extent to which a substance will dissolve in another varies greatly with different substances, and depends on the nature of the solute and solvent, the temperature, and the pressure. In general the effect of pressure on solubility is small unless gases are involved. However, the effect of temperature is usually very pronounced. The direction in which the solubility of a substance in a solvent changes with temperature depends on the heat of solution. If a substance dissolves at saturation with evolution of heat, the solubility decreases with temperature. On the other hand, if a substance dissolves with absorption of heat, the solubility increases as the temperature is raised.

Our knowledge of intermolecular forces is at present too meager to foretell quantitatively the extent of solubility of one substance in another as a function of the chemical nature of solute and solvent. All that can be said is that in general compounds of similar chemical character are more readily soluble in each other than are those whose chemical character is entirely different. When a similarity of chemical nature exists between two substances, the solution of the two will have an environment which will not be too different from that of the pure substances, and the two can tolerate each other in solution. On the other hand, when the chemical nature of the two substances is considerably different, the two substances cannot tolerate each other, and hence there is little tendency to dissolve. Between these two extremes there may be a considerable number of intermediate stages of similarity which will account for the wide ranges of solubility of various substances in each other.

These points may be illustrated with the phenomena encountered in the mutual solubility of liquids. When ethyl alcohol and water, which are closely related chemically, are mixed, the two dissolve in each other in all proportions, i.e., there is no saturation limit. Such substances are said to be *completely miscible*. In distinction to these, two liquids such as water and mercury, which are very different chemically, do not dissolve in each other at all, and are said to be *completely immiscible*.

Between these two limiting types there are liquid pairs, such as ether and water, which dissolve in each other to a limited extent only. Thus, pure ether dissolves a certain amount of water to form a saturated solution of water in ether, while water dissolves a limited amount of ether to form a saturated solution of ether in water. Consequently, with high proportions of one or the other of these liquids, a completely miscible solution can be obtained. When the proportions taken are outside these saturation limits, however, two layers are obtained, one composed of a solution of ether in water, the other of water in ether. Liquid pairs of this sort are said to be *partially miscible*.

Concentration of Solutions. The concentration of the constituents of a solution can be expressed in many different ways. The following list enumerates the more common of these:

- (1) Per cent by weight.
- (2) Per cent by volume.
- (3) Weight of solute per definite weight of solvent.
- (4) Weight of solute per definite weight of solution.
- (5) Molarity — number of moles of solute per liter of solution.
- (6) Normality — number of equivalents of solute per liter of solution.
- (7) Molality — number of moles of solute per 1000 grams of solvent.
- (8) Mol fraction.

All these schemes are either self-explanatory or familiar to the student. As in gas mixtures,¹ the mol fraction of any constituent of a solution is defined as the number of moles of the particular substance present divided by the *total* number of moles of all constituents of the solution. If instead of the number of moles the weights of the constituents are given, the mol fractions can be calculated provided the molecular weights are known, for

$$N_A = \frac{n_A}{n_A + n_B + \dots} = \frac{\frac{W_A}{M_A}}{\frac{W_A}{M_A} + \frac{W_B}{M_B} + \dots} \quad (1)$$

where the W 's are the weights of the various species and the M 's the respective molecular weights.

The choice of a particular method for expressing concentrations depends entirely on convenience and the purpose at hand. Of the various methods listed above, those expressed on a weight basis, namely, the first, third, fourth, seventh, and eighth, are temperature independent, i.e., the concentrations will be the same at all temperatures. The concentrations expressed on a volume basis, however, such as percentage

¹ See page 16.

16TH
EDITION

Remington's

ARTHUR OSOL

*Editor, and Chairman
of the Editorial Board*

EXHIBIT SD-II

Pharmaceutical Sciences

1980

MACK PUBLISHING COMPANY

Easton, Pennsylvania 18042

the salt form and the use of Eq. 11 would be valid for the prediction of solubility. On the other hand, at pH values less than the pH of maximum solubility, the solution would be saturated with salt form and Eq. 11 is no longer really valid. Since in this situation the total solubility of the base, $S_{t(B)}$ is

$$S_{t(B)} = [B] + [BH^+]_s$$

where the subscript s designates a solution saturated with salt, the correct equation to use at pH values less than the pH maximum would be

$$S_{t(B)} = [BH^+]_s \left(1 + \frac{[OH^-]}{K_b} \right) = [BH^+]_s \left(1 + \frac{K_w}{K_b [H^+]} \right) \quad (12)$$

An equation similar to Eq. 12 can likewise be developed for an acidic drug at pHs greater than its pH of maximum solubility.

Modes of Effecting Solution of Solids at the Prescription Counter—The method usually employed by the pharmacist when soluble compounds are to be dissolved in water in compounding a prescription is one which requires the use of the mortar and pestle. The ordinary practice is to crush the substance into fragments in the mortar with the pestle and pour the solvent on it, meanwhile stirring with the pestle until solution is effected. If definite quantities are used, and the whole of the solvent is required to dissolve the given weight of the salt, a portion only of the solvent should be added at first, and when this is saturated the solution is poured off and a fresh portion of solvent added. This operation is repeated until the solid is entirely dissolved; the solutions are then mixed. Other methods of effecting solution are to shake the solid with the liquid in a bottle or flask, or to apply heat to the substances in a suitable vessel. Substances vary greatly in the rate at which they dissolve; some are capable of producing a saturated solution quickly, others require several hours for attainment of saturation. All too often in their haste to prepare a saturated solution pharmacists fail to obtain the required degree of solution of solute.

With hygroscopic substances like pepsin, silver protein compounds, and some others, the best method of effecting solution in water is to place the substance directly upon the surface of the water and then stir vigorously with a glass rod. If the ordinary procedure, such as using a mortar and pestle, is employed with these substances, gummy lumps are formed which are exceedingly difficult to dissolve.

The solubility of chemicals and the miscibility of liquids are important physical factors for the pharmacist to know, as they often have a bearing on the intelligent and proper filling of prescriptions. Mainly for the information of the pharmacist, the USP provides tabular data indicating the degree of solubility or miscibility of many official substances.

Determination of Solubility—For the pharmacist and pharmaceutical chemist the question of solubility is of paramount importance. Not only is it necessary to know solubilities in connection with the preparation and dispensing of medicines, but such information is necessary to effect separation of substances in qualitative and quantitative analysis. Furthermore, the accurate determination of the solubility of a substance is one of the best methods for determining its purity.

The details of the determination of the solubility are markedly affected by the physical and chemical characteristics of the solute and solvent and also by the temperature at which the solubility is to be determined. Accordingly it is not possible to describe a universally applicable method but, in general, the following must be observed in solubility determinations.

1. Purity of both the dissolved substance and the solvent is essential, since impurities in either affect the solubility to a greater or lesser extent.
2. Constancy of temperature must be accurately maintained during the course of the determination.
3. Complete saturation must be attained.
4. Accurate analysis of the saturated solution and correct expression of the results are imperative.

Consideration should be given also to the varying rates of solution of different compounds, and to the marked effect of the degree of fineness of the particles on the time required for the saturation of the solution.

Many of the solubility data of USP have been determined with regard to the exacting requirements mentioned above.

Method for Determining Solubilities—In brief, this consists in preparing a saturated solution of the given substance and ascertaining, by analysis, the amount present in a definite quantity of the solution. Complete saturation can be attained most readily by constant stirring or agitation. A simple apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature. The solvent and excess of solids are placed in the tube and stirred by means of a motor-driven rotating glass spiral. After a given period of stirring, a definite weight of the clear solution is analyzed and the stirring continued for an additional period of several hours. If analysis shows no increase of dissolved substance after the second period of stirring, the result is to be taken as the solubility at the particular temperature. Details of methods for determining solubilities are described in textbooks on experimental physical chemistry.

Phase Solubility Analysis—The procedure of *Phase Solubility Analysis* is one of the most useful and accurate methods for the determination of the purity of a substance. It involves the application of precise solubility methods to the principle that constancy of solubility, in the same manner as constancy of melting point, indicates that a material is pure or free from foreign admixture. It is important to recognize that the technique can be used to obtain the exact solubility of the pure substance without the necessity for the experimental material itself to be pure.

The method is based on the thermodynamic principles of heterogeneous equilibria which are among the soundest of theoretical concepts of chemistry. Thus it is not dependent on any assumptions regarding kinetics or structure of matter, but applicable to all species of molecules, and is sufficiently sensitive to distinguish between optical isomers unless they be present in the ratio of 1:1. The requirements for an analysis are simple since the equipment needed is basic to most laboratories and the quantities of substances required are small.

The standard solubility method consists of five steps:

1. Mixing, in separate systems, increasing amounts of a substance with measured amounts of a solvent.
2. Establishment of equilibrium for each system at identical constant temperature and pressure.
3. Separation of the solid phase from the solutions.
4. Determination of the concentration of the material dissolved in the various solutions.
5. Plotting the concentration of the dissolved material per unit of solvent (y-axis, or solution concentration) against the mass of material per unit of solvent (x-axis or system concentration).

The solubility method has been established on the sound theoretical principles of the Gibbs phase rule: $F = C - P + 2$, which relates C , the number of components, F , the degrees of freedom (pressure, temperature, and concentration), and P , the number of phases for a heterogeneous equilibrium. Since solubility analyses are carried out at constant temperature and pressure, a pure solid in solution would show only one degree of freedom, because only one phase is present at concentrations below saturation. This is represented by